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Efficient one pot preparation of novel 1-oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid derivatives in a green solvent

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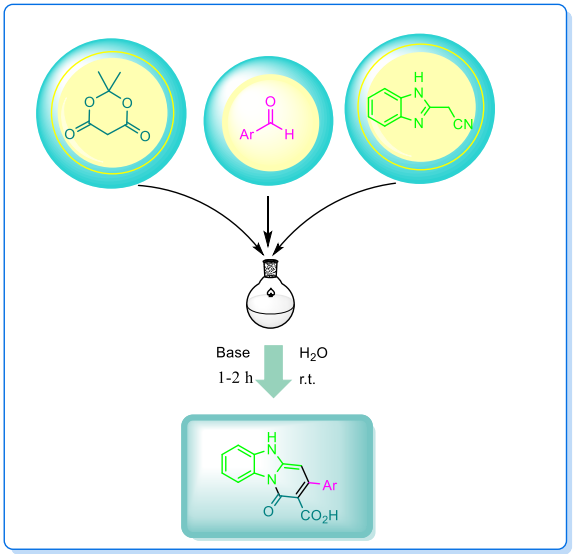
Abstract

Herein we describe a convenient strategy for the synthesis of substituted benzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acids through the one pot, three component reaction of 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile, aryl aldehydes, and Meldrum's acid. The described synthetic route offers an easy access to the title compounds using green chemistry protocols.



Keywords: 1-Oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid, aryl aldehydes, Meldrum's acid, 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile, one pot-three component reactions

Introduction

Because of the rigid character of nitrogen-containing polycyclic compounds, the three dimensional conformation of the molecule is restricted and hence a particular biological activity could be expected.[1] These compounds are characterized by their ability to complex with a multitude of receptors through a variety of favourable interactions. Therefore, the nitrogen-containing heterocyclic compounds are considered very attractive templates for drug discovery. Among various N-containing heterocycles, fused benzimidazoles,[2] are important structural motifs found in numerous natural products and pharmaceutically important compounds.[3] These compounds are the core of many strategic and widely used drugs that have received excellent feedback in the medical and the chemical field as efflux pumps Inhibitors **A**,[4] GABA-A receptors (RWJ-16979) **B**,[5] adrenoreceptors **C**,[6] RWJ-51204 **D**,[7] and fluorescence microscopy **E**.[8] Also, these compounds have biological properties such as anxiolytic agents,[5] anticonvulsive,[9] antimicrobial,[10] relaxant agents,[5] as cell proliferation inhibitors or quadruplex nucleotide stabilizers in DNA,[11] anticancer,[12] antimalarial agents,[13] and human estrogenic receptor activators (Figure 1).[14]

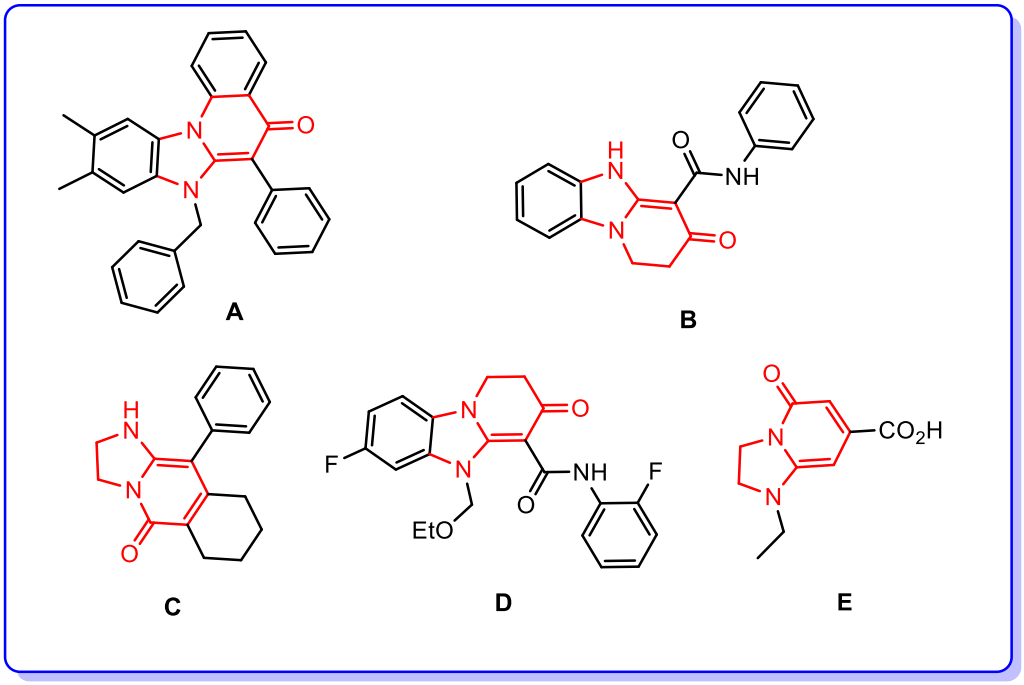


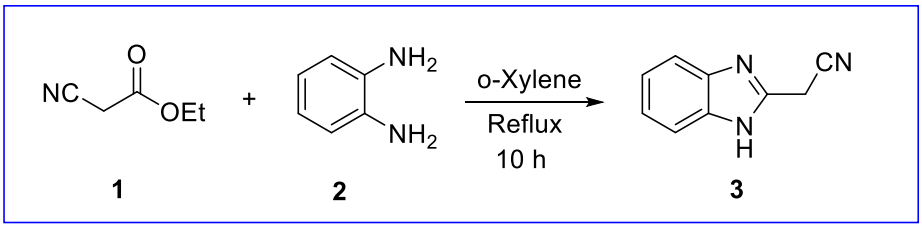
Figure 1. Example of biologically active compounds containing imidazo[3,2-*a*]pyridine fused heterocycle frameworks.

Because the benzo[4,5]imidazo[1,2-*a*]pyridine scaffold show interesting biological activities, the synthesis of this group of compounds has been realised via several routes, including cycloaddition reactions,[6,9,15] condensation reactions,[16-18] multicomponent reactions,[10,19-23] and multistep approaches.[5,24-26] Also, metallic and non-metallic catalysts,[27-30] microwave irradiation,[31] and a series of transition metal catalysts have been used for the preparation of these compounds.[1,32] No doubt, the existing methods are useful, but also possess certain limitations such as an extended reaction time, special apparatus, high temperature, expensive catalysts, toxic solvents, and tedious workup processes.

Given the biological activity of imidazo[1,2-*a*]pyridine-3-carboxamides,[33,34] we decided to synthesize benzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acids, which could be used as the precursor for the preparation of the corresponding lactam derivatives. In this regard, in continuation of our previous work on the development of multicomponent reactions for the synthesis of imidazo[1,2-*a*]pyridines,[35,36] we herein describe a facile and efficient strategy for the synthesis of 1-oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid derivatives *via* the one pot-three component reaction of 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile, aryl aldehydes, and Meldrum's acid in water at room temperature.

Results and Discussion

Our study began with the reaction of ethyl 2-cyanoacetate (**1,** 1.0 mmol**)** and 1,2-phenylenediamine (**2,** 2.0 mmol) to give 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile following a literature procedure (Scheme 1).[37]

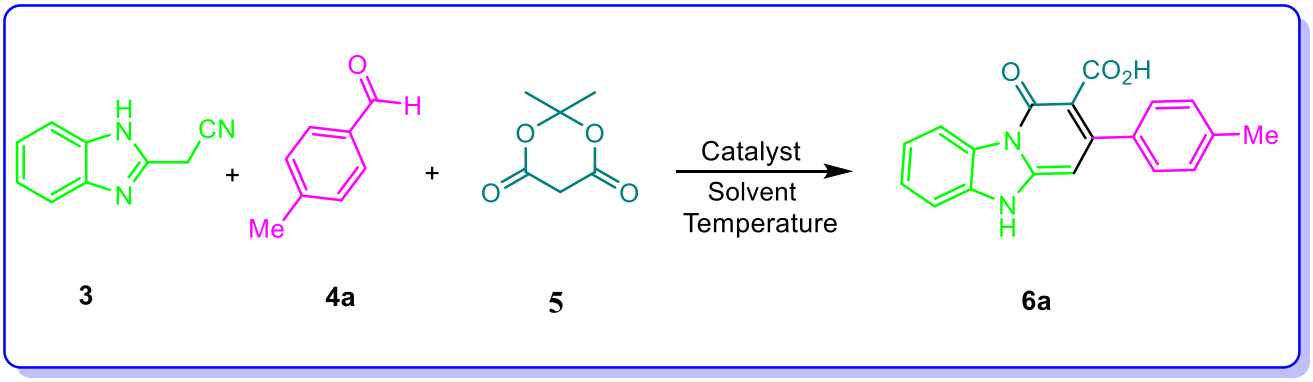


Scheme 1. Synthesis of 2-(1*H*-benzo[d]imidazol-2-*yl*)acetonitrile.

To find the optimized conditions, we examined the synthesis of 1-oxo-3-(*p*-tolyl)-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid **6a** *via* the three component reaction of 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile **3** with 4-methyl benzaldehyde **4a** and Meldrum's acid **5** under a variety of conditions (Table 1).

The optimization of the reaction conditions, including solvent, catalyst, and temperature was investigated. First, various solvents such as water, EtOH, CH_3CN, THF, DMSO, DMF, MeOH, and toluene were examined and water proved to be the solvent of choice for this reaction. Then, the reaction was investigated at different temperatures and room temperature was found to be the best. Then, the reaction was carried out in the presence of piperidine as catalyst at room temperature in water (Table 1, entry 10). The presence of piperidine in the reaction mixture resulted in an increased efficiency, i.e. from 40% to 73%. It was found that prolonging the time of the reaction in the presence of piperidine at room temperature did not improve the yield (Table 1, entry 11). Eventually, a series of experiments revealed that the optimal results were obtained when the reaction of 4-methyl benzaldehyde (**4a**, 1.0 mmol) was conducted with Meldrum's acid (**5**, 1.0 mmol), and 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile (**3**, 1.0 mmol) in presence of piperidine (0.3 mmol) in water at room temperature. Under these optimized conditions, the yield of **6a** reached 73%.

Table 1. Optimization of the reaction conditions in the synthesis of **6a**

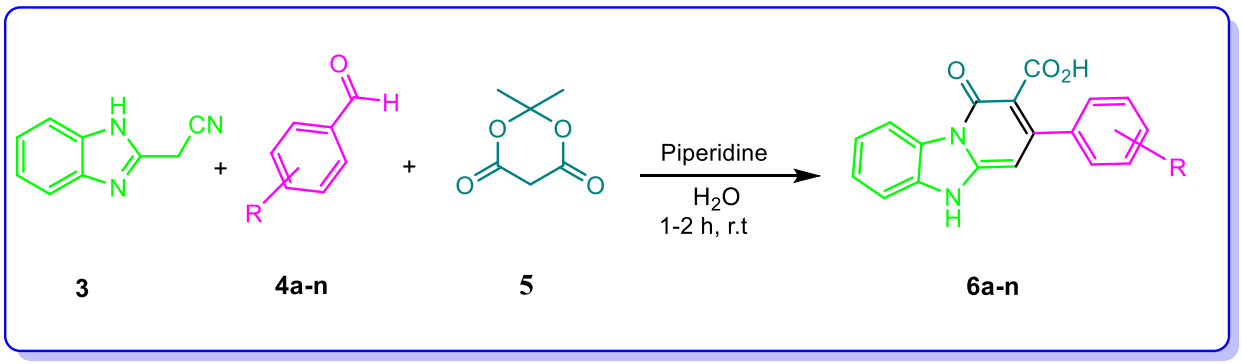


Entry	Solvent	Catalyst	Temp.[a]	Yield (%)[b]
1	EtOH	-	0-4 ˚C	-
2	DMSO	piperidine	r.t	-
3	Toluene	piperidine	r.t	-
4	DMF	piperidine	Reflux	-
5	CH_3CN	piperidine	Reflux	-
6	MeOH	piperidine	Reflux	Trace
7	EtOH	piperidine	Reflux	20
8	AcOH	-	Reflux	Trace
9	H_2O	-	r.t	40
10	H_2O	piperidine	r.t[c]	73
11	H_2O	piperidine	r.t[d]	73

[a]Reaction conditions: solvent 5.0 mL, 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile (**3**, 1.0 mmol), 4-methyl benzaldehyde (**4a**, 1.0 mmol), Meldrum's acid (**5**, 1.0 mmol), piperidine (0.3 mmol), reaction time was 2 h
[b]Isolated yields
[c]Reaction time was 2 h
[d]Reaction time was 24 h

Under these optimized reaction conditions, a series of 1-oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid derivatives **6a–n** were synthesized through Meldrum's acid, different aryl aldehydes, and 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile (Table 2). All the synthesized compounds were previously unknown to the best of our knowledge and were characterized by ^{1}H and ^{13}C NMR, FT-IR, CHN analysis, and melting points. The FT-IR spectrum of 1-oxo-3-(*p*-tolyl)-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid **6a** showed an absorption band at 3419 cm^{-1} for the NH group and absorption bands at 1628 cm^{-1} for the lactam group and 1711 cm^{-1} for the acidic group. In the ^{1}H NMR spectrum of compound **6a** appears one singlet at δ= 1.86 ppm for the methyl group, and two multiplets at δ= 6.64-6.66 and 7.01 ppm for the aromatic protons. The rest of the aromatic protons appear as two doublets at δ= 6.76 and 7.31 ppm with a coupling constant of 7.8 Hz, and one singlet at δ= 7.70 ppm. One singlet and a broad singlet appear at 12.07 and 13.46 ppm for the NH and OH, respectively. The ^{13}C NMR spectrum of compound **6a** showed 17 distinct signals in agreement with the proposed structure. Spectral information of other products is given in the experimental section.

Table 2. Synthesis of 1-oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid **6a–n**



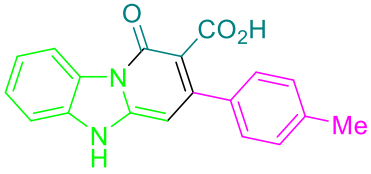
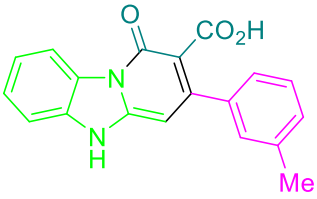
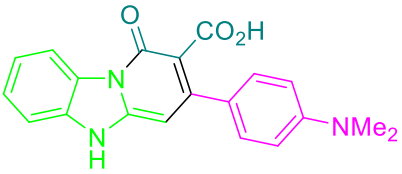
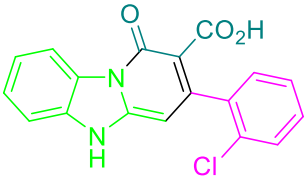
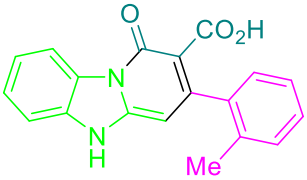
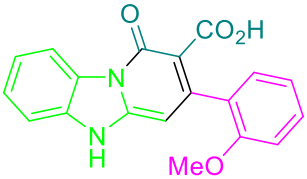
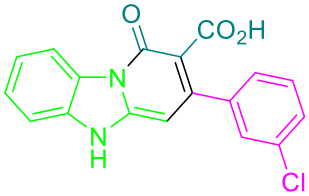
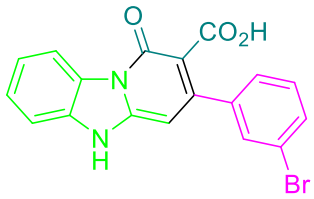
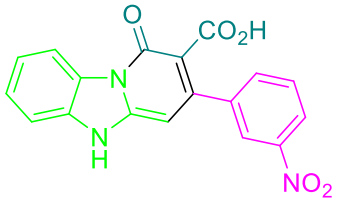
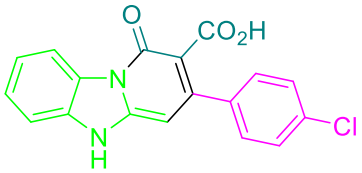
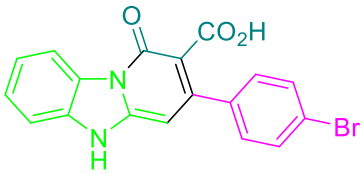
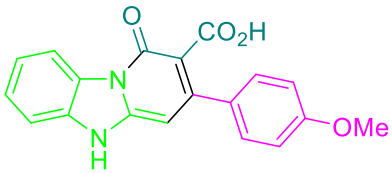
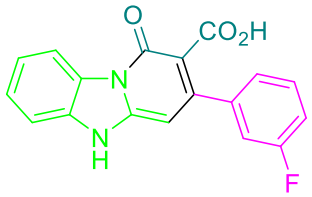
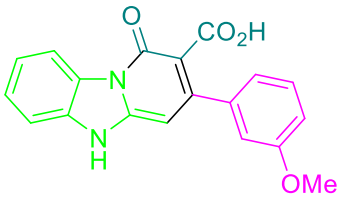
Compound	R	Product	Time (h)	Yield (%)[a]
6a	4-Me		2	73
6b	3-Me		2	72
6c	4-NMe_2		2	70
6d	2-Cl		1	80
6e	2-Me		2	69
6f	2-OMe		1.5	74
6g	3-Cl		1	79

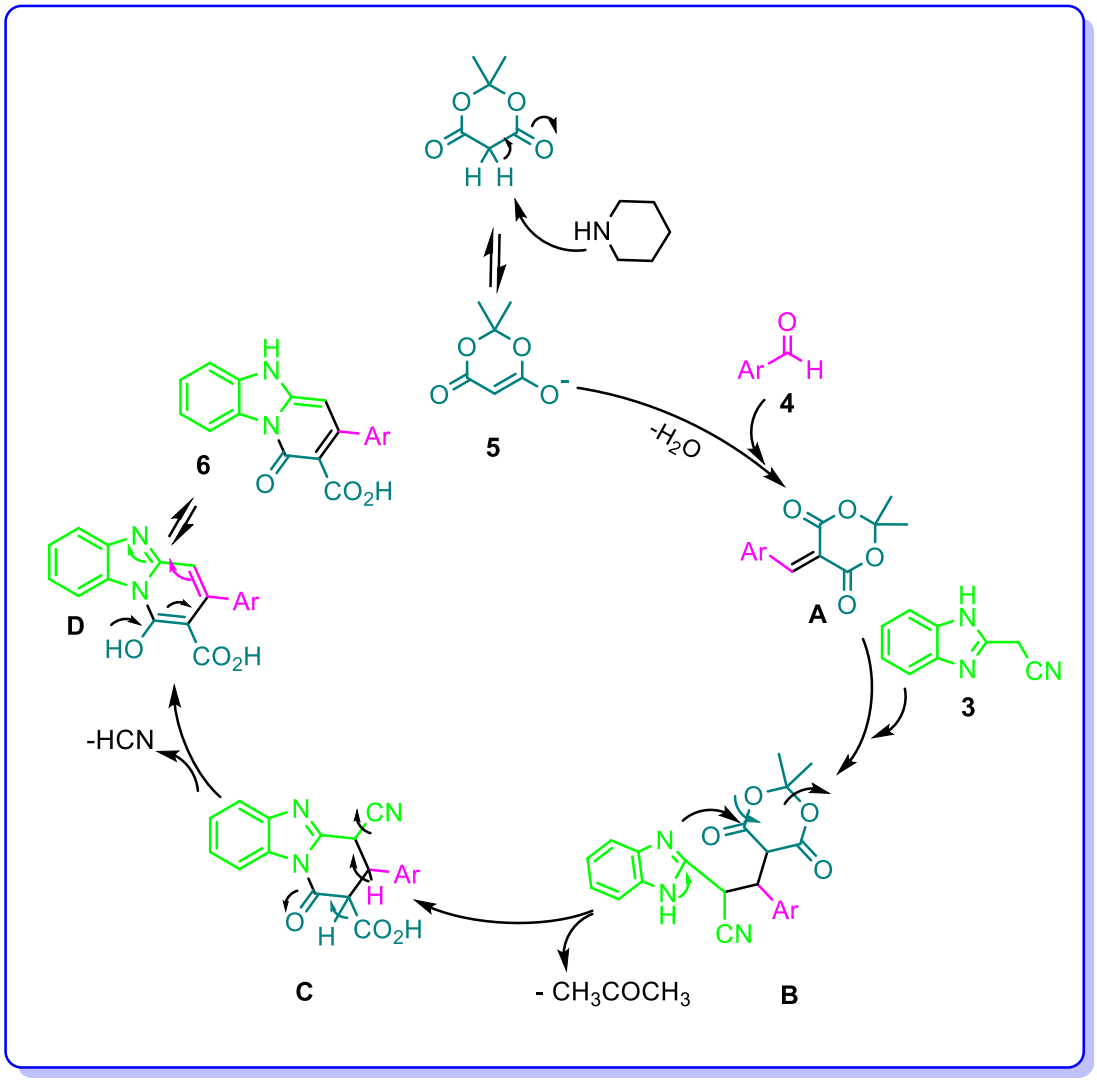
Table 2. Continued

Compound	R	Product	Time (h)	Yield (%)[a]
6h	3-Br		1	78
6i	3-NO_2		1	82
6j	4-Cl		1	81
6k	4-Br		1	80
6l	4-OMe		1.5	75
6m	3-F		1.5	79
6n	3-OMe		1.5	76

[a]Isolated yield: reaction conditions: solvent was 5.0 mL water, 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile (**3**, 1.0 mmol), aryl aldehyde (**4**, 1.0 mmol), Meldrum's acid (**5**, 1.0 mmol), piperidine (0.3 mmol), reaction time was 1-2 h

The reaction was performed in water at room temperature, and after 1-2 hours, products **6a-n** were obtained with a yield of 69-82%. As can be seen from Table 2, electronic effects and the nature of the substituents on the aromatic ring resulted in products with different reaction times and yields. When aromatic aldehydes containing electron-donating groups (such as methyl, methoxy or dimethylamino) were employed, a lower yield and a longer reaction time was required than for those with electron-withdrawing groups (such as nitro or halides) on the aromatic ring.

A proposed mechanism for the formation of 1-oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid **6** is described in Scheme 2. The proposed mechanism for the synthesis of compounds **6** is described in five steps. In this way, initially, the piperidine base abstracts the acidic proton of Meldrum's acid and forms the enol form. Then, an intermediate **A** is prepared from the Knoevenagel condensation between the enol form **5** and aryl aldehyde **4**. Subsequently, compound **B** is prepared through Michael addition of 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile **3** to the intermediate **A**. Then, the intermediate **C** is obtained by intramolecular cyclization and elimination of one molecule of acetone. In the last step, elimination of hydrogen cyanide and aromatization leads to the products **6**.



Scheme 2. The proposed mechanism for the reaction.

Conclusions

In summary, we have shown that 1-oxo-3-aryl-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acids can be efficiently synthesized by reaction of 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile, aryl aldehydes, and Meldrum's acid in the presence of piperidine in water at room temperature for 1-2 h. The presence of

piperidine in the reaction increases the rate of the formation of the arylidene Meldrum's acid, and thus increases the overall rate of the reaction and the final efficiency. In addition, this protocol has advantages in terms of the high yields obtained, the low cost of the starting materials, the short reaction time, the easy work-up, and the use of a green solvent for this synthesis. These products could be used as precursor for the preparation of the corresponding lactams for the development of bioactive agents.

Experimental Section

General. All chemicals were purchased from Aldrich and Merck with high-grade quality and used without any purification. All melting points were obtained using a Barnstead Electrothermal 9200 apparatus and are uncorrected. FT-IR spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr (absorption in cm^{-1}). All the NMR spectra were recorded on a Varian model UNITY Inova 500 MHz spectrometer (^1H: 500, ^{13}C: 125 MHz) in DMSO using TMS as an internal standard. Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectral and physical data.

General procedure for the synthesis of compounds 6a-n. A mixture of 2-(1*H*-benzo[*d*]imidazol-2-*yl*)acetonitrile (**3**, 1.0 mmol), aryl aldehyde (**4**, 1.0 mmol), and Meldrum's acid (**5**, 1.0 mmol), were stirred in the presence of piperidine (0.3 mmol) in water (5.0 mL) at room temperature for 1-2 h. After completion of the reaction, determined by TLC, The crude product was filtered. The crude product is purified by recrystallization in ethanol.

1-Oxo-3-(*p*-tolyl)-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6a). Yellow solid; yield 73%; mp: 198-200 °C. IR: 3419, 3065, 1711, 1628 cm^{-1}. ^1H NMR: δ 1.86 (s, 3H, CH_3), 6.64-6.66 (m, 2H, ArH), 6.76 (d, *J* 7.9 Hz, 2H, ArH), 7.01 (m, 2H, ArH), 7.31 (d, *J* 7.9 Hz, 2H, ArH), 7.70 (s, 1H, ArH), 12.07 (s, 1H, NH), 13.46 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 21.1, 100.8, 108.4, 110.0, 112.3, 116.0, 122.6, 123.0, 129.3, 129.4, 130.1, 141.7, 141.9, 145.0, 146.0, 147.3, 162.5 ppm. Anal. Calcd for $C_{19}H_{14}N_2O_3$ (318.33): C, 71.69; H, 4.43; N, 8.80. Found: C, 71.92; H, 4.48; N, 8.68.

1-Oxo-3-(*m*-tolyl)-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6b). Yellow solid; yield 72%; mp: 205-207 °C. IR: 3402, 3056, 1716, 1590 cm^{-1}. ^1H NMR: δ 2.39 (s, 3H, CH_3), 7.18 (d, *J* 3.1 Hz, 1H, ArH), 7.19 (d, *J* 3.1 Hz, 1H, ArH), 7.29 (d, *J* 7.5 Hz, 1H, ArH), 7.41 (t, *J* 7.6 Hz, 1H, ArH), 7.59 (m, 2H, ArH), 7.96 (d, *J* 8.7 Hz, 1H, ArH), 8.03 (s, 1H, ArH), 12.97 (broad, s, 1H, NH), 14.93 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 21.4, 92.6, 103.2, 114.7, 114.9, 122.4, 124.0, 127.4, 129.2, 130.5, 130.9, 133.4, 133.6, 137.0, 138.6, 141.7, 151.8, 164.6, 177.0 ppm. Anal. Calcd for $C_{19}H_{14}N_2O_3$ (318.33): C, 71.69; H, 4.43; N, 8.80. Found: C, 71.48; H, 4.38; N, 8.84.

3-(4-(Dimethylamino)phenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6c). Yellow solid; yield 70%; mp: 232-234 °C. IR: 3253, 3044, 1719, 1613 cm^{-1}. ^1H NMR: δ 3.04 (s, 3H, CH_3), 6.84 (d, *J* 9.0 Hz, 2H, ArH), 7.19 (m, 2H, ArH), 7.54 (m, 2H, ArH), 7.89 (d, *J* 9.0 Hz, 2H, ArH), 8.11 (s, 1H, ArH), 12.65 (s, 1H, NH), 13.97 (broad, s, 1H, OH) ppm, ^{13}C NMR: δ 53.2, 56.1, 94.3, 111.6, 112.2, 118.1, 119.1, 120.3, 122.4, 122.8, 123.1, 132.3, 135.4, 144.0, 145.9, 149.3, 152.9, 155.2 ppm. Anal. Calcd for $C_{20}H_{17}N_3O_3$ (347.37): C, 69.15; H, 4.93; N, 12.10. Found: C, 69.34; H, 4.97; N, 12.06.

3-(2-Chlorophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6d). Yellow solid; yield 80%; mp: 240-242 °C. IR: 3449, 3062, 1688, 1621 cm^{-1}. ^1H NMR: δ 7.20-7.24 (m, 2H, ArH), 7.48-7.56 (m, 4H, ArH), 7.64 (d, *J* 7.5 Hz, 1H, Ar), 7.69 (d, *J* 7.7 Hz, 1H, ArH), 7.89 (d, *J* 7.5 Hz, 1H, ArH), 12.68 (s, 1H, NH), 13.77 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 98.9, 112.1, 118.9, 119.5, 122.1, 123.1, 127.8, 130.4, 130.7,131.6,

132.1, 132.5, 135.1, 137.4, 143.7, 149.5, 152.6, 166.6 ppm. Anal. Calcd for $C_{18}H_{11}ClN_2O_3$ (338.75): C, 63.82; H, 3.27; N, 8.27. Found: C, 63.70; H, 3.31; N, 8.16.

1-Oxo-3-(*o*-tolyl)-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6e). Yellow solid; yield 69%; mp: 196-198 °C. IR: 3412, 3052, 1742, 1614 cm^{-1}. ^1H NMR: δ 2.31 (s, 3H, CH_3), 7.22-7.27 (m, 4H, ArH), 7.30 (t, *J* 7.6 Hz, 1H, ArH), 7.62-7.64 (m, 2H, ArH), 7.86 (d, *J* 7.7 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 12.19 (s, 1H, NH), 14.04 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 20.6, 103.1, 116.9, 121.6, 122.9, 123.1, 123.6, 127.4, 128.7, 129.0, 131.0, 140.5, 145.6, 155.3, 162.5, 165.6, 169.6, 176.6, 177.2 ppm.

3-(2-Methoxyphenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6f). Yellow solid; yield 74%; mp: 223-225 °C. IR: 3423, 3053, 1721, 1620 cm^{-1}. ^1H NMR: δ 4.06 (s, 3H, OCH_3), 7.06 (d, *J* 8.4 Hz, 1H, ArH), 7.14 (t, *J* 7.4 Hz, 1H, ArH), 7.25-7.27 (m, 3H, ArH), 7.42 (t, *J* 6.8 Hz, 1H, ArH), 7.66 (m, 2H, ArH), 8.59 (d, *J* 7.8 Hz, 1H, ArH), 10.53 (s, 1H, NH), 14.53 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 54.3, 96.1, 110.1, 111.5, 115.1, 117.9, 121.7, 122.5, 129.1, 130.2, 131.1, 136.5, 137.9, 139.5, 149.8, 156.8, 156.8, 171.9, 172.3 ppm. Anal. Calcd for $C_{19}H_{14}N_2O_4$ (334.33): C, 68.26; H, 4.22; N, 8.38. Found: C, 68.54; H, 4.27; N, 8.35.

3-(3-Chlorophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6g). Yellow solid, yield 79%; mp: 237-239 °C. IR: 3449, 3045, 1684, 1631 cm^{-1}. ^1H NMR: δ 7.18-7.25 (m, 2H, ArH), 7.52-7.59 (m, 4H, ArH), 7.66 (d, *J* 7.8 Hz, 1H, ArH), 8.13 (d, *J* 7.4 Hz, 1H, ArH), 8.21 (s, 1H, ArH), 13.03 (s, 1H, NH), 14.96 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 106.3, 110.4, 111.9, 119.5, 122.3, 123.4, 125.4, 126.4, 127.1, 129.9, 131.3, 132.7, 134.2, 135.4, 137.8, 144.1, 150.2, 177.6 ppm.

3-(3-Bromophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6h). Yellow solid; yield 78%; mp: 239-241 °C. IR: 3412, 3094, 1731, 1601 cm^{-1}. ^1H NMR: δ 7.18 (d, *J* 3.1 Hz, 1H, ArH), 7.20 (d, *J* 3.1 Hz, 1H, ArH), 7.45-7.48 (m, 1H, ArH), 7.58-7.59 (m, 2H, ArH), 7.63 (d, *J* 6.8 Hz, 1H, ArH), 8.17 (d, *J* 6.65 Hz, 1H, ArH), 8.36 (s, 1H, ArH), 12.87 (s, 2H, NH, OH) ppm, ^{13}C NMR: δ 115.3, 120.1, 122.6, 122.8, 125.7, 126.0, 127.2, 128.8, 129.4, 130.8, 131.4, 131.5, 131.6, 132.0, 132.7, 132.8, 150.0, 166.9 ppm. Anal. Calcd for $C_{18}H_{11}BrN_2O_3$ (383.20): C, 56.42; H, 2.89; N, 7.31. Found: C, 56.70; H, 2.93; N, 7.24.

3-(3-Nitrophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6i). Yellow solid; yield 82%; mp: 259-261 °C. IR: 3436, 3093, 1737, 1613 cm^{-1}. ^1H NMR: δ 7.22-7.26 (m, 3H, ArH), 7.56 (d, *J* 7.8 Hz, 1H, ArH), 7.70 (d, *J* 7.8 Hz, 1H, ArH), 7.83 (t, *J* 8.0 Hz, 1H, ArH), 8.30 (d, *J* 7.1 Hz, 1H, ArH), 8.60 (d, *J* 7.1 Hz, 1H, ArH), 9.00 (s, 1H, ArH), 13.21 (s, 1H, NH), 13.86 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 100.8, 112.1, 114.9, 119.7, 121.3, 122.5, 123.7, 124.6, 131.1, 132.2, 132.9, 135.5, 144.2, 148.7, 149.5, 157.1, 171.6, 173.4 ppm. Anal. Calcd for $C_{18}H_{11}N_3O_5$ (349.30): C, 61.89; H, 3.17; N, 12.03. Found: C, 62.03; H, 3.20; N, 12.08.

3-(4-Chlorophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6j). Yellow solid; yield 81%; mp: 234-236 °C. IR: 3413, 3001, 1725, 1626 cm^{-1}. ^1H NMR: δ 7.26 (m, 2H, ArH), 7.61-7.63 (m, 2H, ArH), 7.65 (d, *J* 8.3 Hz, 2H, ArH), 7.98 (d, *J* 8.3 Hz, 2H, ArH), 8.32 (s, 1H, ArH), 12.67 (s, 1H, NH), 13.52 (broad, s, 1H, OH) ppm. ^{13}C NMR: δ 93.8, 103.6, 116.4, 120.0, 123.6, 129.4, 129.8, 131.6, 132.0, 136.6, 138.1, 144.4, 145.7, 147.3, 158.6, 167.2 ppm. Anal. Calcd for $C_{18}H_{11}ClN_2O_3$ (338.75): C, 63.82; H, 3.27; N, 8.27. Found: C, 63.74; H, 3.34; N, 8.13.

3-(4-Bromophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6k). Yellow solid; yield 80%; mp: 241-243 °C. IR: 3452, 3095, 1734, 1665 cm^{-1}. ^1H NMR: δ 7.24-7.25 (m, 2H, ArH), 7.60-7.62 (m, 2H, ArH), 7.79 (d, *J* 8.6 Hz, 2H, ArH), 7.89 (d, *J* 8. Hz, 2H, ArH), 8.29 (s, 1H, ArH), 12.77 (s, 2H, NH, OH) ppm. ^{13}C NMR: δ 103.6, 110.0, 112.1, 114.9, 116.3, 124.2, 125.5,131.7, 132.3, 132.7, 133.8, 137.3, 139.4, 144.5, 147.6, 152.6 ppm.

3-(4-Methoxyphenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6l). Yellow solid; yield 75%; mp: 224-226 °C. IR: 3420, 3097, 1708, 1632 cm^{-1}. ^1H NMR: δ 3.84 (s, 3H, OCH_3), 7.12 (d, *J* 8.6 Hz, 2H, ArH), 7.19 (d, *J* 4.2 Hz, 1H, ArH), 7.21 (d, *J* 4.2 Hz, 1H, ArH), 7.57 (d, *J* 3.2 Hz, 1H, ArH), 7.59 (d, *J* 3.2 Hz, 1H,

ArH), 7.98 (d, *J* 8.6 Hz, 2H, ArH), 8.40 (s, 1H,ArH), 13.27 (broad, s, 1H, NH), 14.07 (broad, s,1H, OH) ppm. ^{13}C NMR: *δ* 56.0, 99.6, 114.1, 115.3, 117.1, 123.1, 124.0, 125.8, 129.9, 131.4, 132.2, 137.8, 145.6, 148.5, 149.8, 159.9, 162.5 ppm

3-(3-Fluorophenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6m). Yellow solid; yield 79%; mp: 228-230 °C. IR: 3267, 3039, 1719, 1627 cm^{-1}. ^{1}H NMR: *δ* 7.20-7.22 (m, 2H, ArH), 7.41 (t, *J* 8.5 Hz, 1H, ArH), 7.59-7.64 (m, 3H, ArH), 7.77-7.80 (m, 2H, ArH), 8.50 (s, 1H, ArH), 12.38 (broad, s, 1H, NH), 14.47 (broad, s, 1H, OH) ppm. ^{13}C NMR: *δ* 108.2, 110.0, 111.9, 119.4, 123.0, 126.5, 128.1, 131.7, 136.5, 136.7, 143.4, 151.3, 152.0, 155.7, 169.1, 172.9, 177.1, 177.2 ppm. Anal. Calcd for $C_{18}H_{11}FN_2O_3$ (322.30): C, 67.08; H, 3.44; N, 8.69. Found: C, 67.32; H, 3.52; N, 8.66.

3-(3-Methoxyphenyl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid (6n). Yellow solid; yield 76%; mp: 225-227 °C. IR: 3424, 3025, 1722, 1629 cm^{-1}. ^{1}H NMR: *δ* 3.43 (s, 3H, OCH_3), 6.62 (d, *J* 7.7 Hz, 1H, ArH), 6.80 (m, 2H, ArH), 6.98 (t, *J* 7.7 Hz, 1H, ArH), 7.05 (d, *J* 7.3 Hz, 1H, ArH), 7.15 (m, 2H, ArH), 7.28 (s, 1H, ArH), 7.85 (s, 1H, ArH), 12.22 (s, 1H, NH), 13.12 (broad, s, 1H, OH) ppm. ^{13}C NMR: *δ* 55.0, 100.9, 101.0, 102.1, 111.5, 113.7, 116.0,117.4, 122.3, 122.7, 129.8, 131.3, 132.6, 133.8, 145.0, 147.0, 159.5, 165.9, 176.6 ppm. Anal. Calcd for $C_{19}H_{14}N_2O_4$ (334.33): C, 68.26; H, 4.22; N, 8.38. Found: C, 68.11; H, 4.19; N, 8.42.

References

1. Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G.; Gajula, B.; Sridhar, B.; Pottireddygari, G. R.; Rao, T. P. *J. Org. Chem.* **2010**, *75*, 5963. https://doi.org/10.1021/jo1013228
2. Chimirri, A.; de Sarro, A.; de Sarro, G.; Gitto, R.; Zappal, M. *Farmaco*, **2001**, *56*, 821. https://doi.org/10.1016/S0014-827X(01)01147-8
3. Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc*. **2008**, *130*, 416. https://doi.org/10.1021/ja077473r
4. Cannalire, R.; Machado, D.; Felicetti, T.; Costa, S. S.; Massari, S.; Manfroni, G.; Cecchetti, V. *Eur. J. Med. Chem.* **2017**, *140*, 321. https://doi.org/10.1016/j.ejmech.2017.09.014
5. Maryanoff, B. E.; Ho, W.; McComsey, D. F.; Reitz, A. B.; Grous, P. P.; Nortey, S. O.; Gardocki, J. F. *J. Med. Chem*. **1995**, *38*, 16. https://doi.org/10.1021/jm00001a005
6. Jones, R. C.; Dimopoulos, P.; Coles, S. C.; Light, M. E.; Hursthouse, M. B. *J. Chem. Soc.* **2000**, *1*, 2331. https://doi.org/10.1039/B001830I
7. Dubinsky, B.; Vaidya, A. H.; Rosenthal, D. I.; Hochman, C.; Crooke, J. J.; DeLuca, S.; Shank, R. P. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 777. https://doi.org/10.1124/jpet.102.034439
8. Zheng, X.; Shao, D.; Li, J.; Song, Y.; Chen, Y.; Pan, Y.; Chen, L. *Rsc. Adv*. **2015**, *5*, 91398. https://doi.org/10.1039/C5RA18391J
9. Bokanov, A. I.; Evstratova, M. I.; Turchin, K. F.; Granik, V. G.; Andreeva, N. I.; Asnina, V. V.; Mashkovskii, M. D. *Pharm. Chem. J.* **1997**, *31*, 532. https://doi.org/10.1021/js960213f
10. Ma, Y. L., Wang, K. M.; Lin, X. R.; Yan. S. J.; Lin. J. *Tetrahedron* **2014**, *70*, 6578. https://doi.org/10.1016/j.tet.2014.07.017

11. O'Brien, S.; Siddiqui-Jain. A.; *WO2007056113A2*. **2007,** 18.
12. Rajput, S.; Gardner, C. R.; Failes, T.W.; Arndt, G. M.; Black, D. S.; Kumar, N. *Bioorg. Med. Chem*. **2014,** *22*, 105.
https://doi.org/10.1016/j.bmc.2014.06.013
13. Cross, R. M.; Flanigan, D. L.; Monastyrskyi, A.; LaCrue, A. N.; Saenz, F. E.; Maignan, J. R.; Mutka, T. S.; White, K. L.; Shackleford, D. M.; Bathurst, I.; Fronczek, F. R.; Wojtas, L.; Guida, W. C.; Charman, S. A.; Burrows, J. N.; Kyle, D. E.; Manetsch, R. *J. Med. Chem.* **2014,** *57*, 8860.
https://doi.org/10.1021/jm500942v
14. Gim, H. J.; Li, H.; Jung, S. R.; Park, Y. J.; Ryu, J. H.; Chung, K. H.; Jeon, R. *Eur. J. Med. Chem.* **2014,** *85*, 107.
https://doi.org/10.1016/j.ejmech.2014.07.030
15. Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368.
https://doi.org/10.1021/jo9915729
16. Nagarajan, K.; Rao, V. R.; Shah, R. K.; Shenoy, S. J.; Fritz, H.; Richter, W. J.; Muller, D. *Helv. Chim. Acta* **1988**, *71*, 77.
https://10.1007/s00044-014-1231-6
17. Rida, S. M.; Soliman, F. S.; Badawey, E. S. A.; Kappe, T. *J. Heterocycl. Chem*. **1988,** *25*, 1725.
https://10,1007/s11030-020-10097-z
18. Soliman, F. S.; Rida, S. M.; Badawy, E. S. A.; Kappe, T. *Arch. Pharm.* **1984,** *317*, 951.
https://doi.org/10.1002/ardp.19843171110
19. Bollini, M.; Casal, J. J.; Asís, S. E.; Leal, E. S.; Bruno, A. M. *Med. Chem. Res.* **2015,** *24*, 1496.
https://doi.org/10.1007/s00044-014-1231-6
20. Bollini, M.; González, M.; Bruno, A. M. *Tetrahedron Lett*. **2009,** *50*, 1507.
https://doi.org/10.1016/j.tetlet.2009.01.083
21. Patel, D. M.; Vala, R. M.; Sharma, M. G.; Rajani, D. P.; Patel, H. M. A. *Chem. Select.* **2019**, *4*, 1031.
https:// doi: 10.1002/slct.201803605
22. Vala, R. M.; Patel, D. M.; Sharma, M. G.; Patel, H. M. *Rsc. Adv.* **2019**, *9*, 28886.
https:// doi: 10.1039/C9RA05975J
23. Patel, D. M.; Sharma, M. G.; Vala, R. M.; Lagunes, I.; Puerta, A.; Padrón, J. M.; Patel, H. M. *Bioorg Chem*. **2019**, *86*, 137.
https://doi.org/10.1016/j.bioorg.2019.01.029
24. Podhorez, D. E. *J. Heterocycl. Chem.* **1991,** *28*, 971.
https://doi.org/10.1002/jhet.5570280422
25. Wang, H.; Peng, L.; Zhao, M.; Liu, J.; Zhang, X.; Wang, Y.; Peng, S. *Bioorgan. Med. Chem.* **2011,** *19*, 871.
https://doi.org/10.1016/j.bmc.2010.12.005
26. Fryšová, I.; Slouka, J.; Gucký, T. *Arkivoc* **2005**, *xv*, 30.
https://doi.org/10.3998/ark.5550190.0006.f05
27. Kavala, V.; Wang, C. C.; Wang, Y. H.; Kuo, C. W.; Janreddy, D.; Huang, W. C.; Yao, C. F. *Adv. Synth. Catal.* **2014,** *356*, 2609.
https://doi.org/10.1039/C9OB02329A
28. Wang, H. C.; Jagtap, A. D.; Chang, P. T.; Liu, J. R.; Liu, C. P.; Tseng, H. W.; Chern, J. W. *Eur. J. Med. Chem.* **2014,** *84*, 312.
https://doi.org/10.1016/j.ejmech.2014.07.033
29. Khurana, J. M.; Sharma, V. *Chem. Heterocycl. Compd.* **2008,** *44*, 309.
https://doi:10.1007/s10593-008-0045-1

30. Sharma, M. G.; Vala, R. M.; Patel, H. M. *Rsc. Adv*. **2020**, *10*, 35499. https://doi.org/10.1039/D0RA06738E
31. Karuvalam, R. P.; Haridas, K. R.; Sajith, A. M.; Pakkath, R.; Bhaskaran, S.; Padusha, M. S. A.; Bakulev, V. A.; Joy, M. N. Arkivoc **2019** ,*vi*, 431. https://doi.org/10.24820/ark.5550190.p011.121
32. Xu, H.; Xu, L.; Luo, X.; Wang, J.; Zhou, X.; Yang, B.; Liao, S. *Tetrahedron* **2019,** *75*, 2785. https://doi.org/10.1016/j.tet.2019.03.058
33. Kai, L.; Linhu, Li.; Wang, B.; Mingliang, L.; Wang, B.; Weiyi, Sh.; Huiyuan, G.; Yu, L. *Eur. J. Med. Chem.* **2017,** *137*, 117. https://doi.org/10.1016/j.ejmech.2017.05.044
34. Apeng, W.; Kai, L.; Linhu, L.; Hongtao, L.; Zeyu, T.; Bin, W.; Mingliang, L.; Chao, M.; Xican, M.; Bing, H.; Aoyu, W.; Yu, L. *Eur. J. Med. Chem*. **2019,** *178*, 715. https://doi.org/10.1016/j.ejmech.2019.06.038
35. Asadi, S.; Zebarjad, M.; Masoudi, H.; Mehrabi, H. *Res. Chem. Intermed*. **2021**, Accepted. https://doi.org/10.1007/s11164-021-04554-z
36. Asadi, S.; Hajipour, M.; Mehrabi, H. *Arkivoc* **2021**, *X*, 27. https://doi.org/10.24820/ark.5550190.p011.601
37. Goli-Garmroodi, F.; Omidi, M.; Saeedi, M.; Sarrafzadeh, F.; Rafinejad, A.; Mahdavi, M.; Foroumadi, A. *Tetrahedron Lett*. **2015,** *56*, 743. https://doi.org/10.1016/j.tetlet.2014.12.099